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REVIEW ARTICLE

The genetics of generalized vitiligo and associated autoimmune diseases

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Summary Generalized vitiligo is an acquired disorder in which patches of depigmented skin, overlying hair, and oral mucosa result from progressive autoimmune loss of melanocytes from the involved areas. Although vitiligo is perhaps the most common pigmentary disorder, insufficiently clear clinical definition of the disorder and lack of a good laboratory animal model have inhibited progress in understanding its pathobiology, its environmental triggers, and in developing specific and effective therapeutic approaches. Vitiligo results from a complex interaction of environmental, genetic, and immunologic factors, which ultimately contribute to melanocyte destruction, resulting in the characteristic depigmented lesions. In the past few years, studies of the genetic epidemiology of generalized vitiligo have led to the recognition that vitiligo is part of a broader, genetically-determined, autoimmune/autoinflammatory diathesis. Attempts to identify genes involved in vitiligo susceptibility have involved both allelic association studies of candidate genes and genome-wide linkage analyses to discover new genes, and these studies have begun to shed light on the mechanisms of vitiligo pathogenesis. It is anticipated that the discovery of biological pathways of vitiligo pathogenesis will provide novel therapeutic and prophylactic targets for future approaches to the treatment and prevention of vitiligo and its associated autoimmune diseases.

Contents

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1. Background

Generalized vitiligo is an acquired, non-contagious disorder in which progressive, patchy loss of pigmentation from skin, overlying hair, and oral mucosa results from loss of melanocytes from the involved areas [1,2] (Fig. 1). Vitiligo is perhaps the most common pigmentary disorder, affecting about 0.38% of Caucasians [3] and occurring with similar frequency throughout the world (e.g. [4]). Various etiologic hypotheses have been suggested [1,2], for which the most compelling evidence involves a combination of environmental, genetic, and immunologic factors interacting to contribute to autoimmune melanocyte destruction. Nevertheless, despite many years of research, the specific causes of generalized vitiligo remain obscure, and no specific common environmental factors that trigger generalized vitiligo, either directly or via an autoimmune response, have yet been identified. This limited progress has resulted, in large part, from lack of a clear definition of the disorder and the lack of a tractable experimental animal model of human vitiligo that can be manipulated and studied in the laboratory.

In recent years, advances in analysis of the human genome have led to efforts to identify specific genes involved in vitiligo susceptibility and pathogenesis. As the result, there has been considerable recent progress towards identification of vitiligo susceptibility genes, some of which may provide novel therapeutic and prophylactic targets for new interventional approaches to treat and prevent vitiligo in the future.

2. Genetic epidemiology

To some extent, the slow progress in vitiligo research has resulted from lack of clarity in defining the disorder and in testing specific hypotheses via carefully controlled studies. It is thus of primary importance to clearly define generalized vitiligo. Generalized vitiligo is characterized by acquired depigmentation due to melanocyte loss, in a pattern that is non-focal and generally bilateral across the midline, though not necessarily symmetric. This definition thus excludes various Mendelian hypopigmentary spotting disorders, such as piebaldism and the various forms of Waardenburg syndrome, which result from mutations in specific single genes and which are characterized by congenital white spotting that is relatively stable over patients' lifetimes [5]. This definition of generalized vitiligo also excludes segmental vitiligo and other localized forms of vitiligo, whose true pathogenic relationship to generalized vitiligo is as-yet unknown, but includes acrofacial vitiligo, which often progresses to more extensive skin involvement and is often associated with other autoimmune/autoinflammatory disorders. The strict definition of generalized vitiligo also excludes many other forms of skin depigmentation, such as depigmentation resulting from contact or occupational exposure to known depigmenting agents, such as phenols, catechols, quinines, and other compounds, depigmentation secondary to chronic inflammation, psoriasis, other forms of dermatitis, and depigmentation secondary to infection, scars, burns, and various other skin insults. This is not to say that these other forms of depigmentation might not share some biological pathways of disease pathogenesis with generalized vitiligo, but strictly defined, they are not vitiligo.

When one applies such a clear definition, the picture of generalized vitiligo comes into much sharper focus. Most cases of generalized vitiligo occur sporadically, but about 20% of patients have one or more affected first-degree relatives. Very rarely, large multi-generation families segregate vitiligo in an autosomal dominant pattern with incomplete penetrance [6]. More typically, however, one sees family clusters of vitiligo cases, occurring in a non-Mendelian pattern that is suggestive of polygenic, multifactorial inheritance [4,7–15]. However, it must be repeated that the great majority of vitiligo patients have no family history of the disorder.

The strongest evidence for genetic factors in the pathogenesis of generalized vitiligo comes from studies of patients' close relatives. In Caucasians, the risk to a patient's siblings is about 6.1% [15], a 16-fold increased relative risk (λ_S) over the 0.38% frequency of generalized vitiligo in the Caucasian population [3]. There is similar risk of generalized vitiligo to patients' other first-degree relatives besides siblings: 7.1% in Caucasians, 6.1% in Indo–Pakistanis, and 4.8% in Hispanics [15], with lower risks to more distant relatives. Additional evidence for a genetic component to generalized vitiligo comes from age of onset data: among unselected